Evidence Reports of Kampo Treatment (EKAT)

Appendix 2011

Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF)
Special Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Edited by

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ver. 1.0, 1 October 2011

History of version upgrades

1 Oct. 2011: Kampo Chiryo Ebidensu Repoto Appendix 2011 (Evidence Reports of Kampo Treatment Appendix 2011)

1 Jun. 2010: Kampo Chiryo Ebidensu Repoto 2010 – 345 no RCT (Evidence Reports of Kampo Treatment 2010: 345 Randomized Controlled Trials)

1 Jun. 2009: Kampo Chiryo Ebidensu Repoto 2009 – 320 no RCT (Evidence Reports of Kampo Treatment 2009: 320 Randomized Controlled Trials)

1 Apr. 2008: Kampo Chiryo Ebidensu Repoto Dai 2 -han – RCT wo Shu ni Shite- Chukan Hokoku 2007 ver 1.1 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007 ver.1.1)

15 Jun. 2007: Kampo Chiryo Ebidensu Repoto Dai 2-han –RCT wo Shu ni Shite- Chukan Hokoku 2007 (Evidence Reports of Kampo Treatment 2nd edition - Focusing on RCTs- Interim Report 2007)

20 Jul. 2005: Kampo Chiryo niokeru Ebidensu Repoto (Evidence Reports of Kampo Treatment) (*Nihon Toyo Igaku Zasshi* [*Kampo Medicine*] 2005: 56, EBM supplementary issue)

20 Sept. 2002: Kampo Chiryo niokeru EBM – 2002 nen Chukan Hokoku (EBM in Kampo 2002, Interim Report) (*Nihon Toyo Igaku Zasshi* [*Japanese Journal of Oriental Medicine*] 2002: 53 [5], supplementary issue)

Notes on the EKAT Appendix 2010

The Task Force for Evidence Reports/Clinical Practice Guidelines (ER/CPG-TF) of the Japan Society for Oriental Medicine (JSOM) Evidence-based Medicine (EBM) Special Committee gathers comprehensive data on the randomized controlled trials (RCTs) of Kampo formulations in Japan, and compiles structured abstracts (SAs) and publishes them as "Kampo Chiryo Ebidensu Repoto (Evidence Reports of Kampo Treatment [EKAT])." As the version history on the previous page shows, the "Kampo Chiryo Ebidensu Repoto 2010 - 345 no RCT-(Evidence Reports of Kampo Treatment: 345 Randomized Controlled Trials (EKAT 2010)" was published on June 1, 2010, and included 345 RCTs and 1 meta-analysis published between 1986, when the specifications for the quality of Kampo formulations for prescription became as they are today, and the first half of 2009.

Undertaking a complete revision including additions and publishing the results each year as EKAT 20xx require a huge amount of manpower and financial resources. The FY 2011 budget of the Japan Society for Oriental Medicine would not allow for the compilation of a fully revised EKAT 2011. The decision was taken to compile this Appendix by searching for RCT papers on November 4, 2010 using the same method as EKAT 2010 and including additions or revisions made since publication of EKAT 2010. Therefore, the combination of EKAT 2010 and this EKAT Appendix 2010 represents the most up-to-date version of EKAT available at present. The purpose and methods adopted in compiling EKAT are described in detail in EKAT 2010.

Contained in this Appendix are 14 structured abstracts of RCT papers that were newly found and 2 structured abstracts already contained in EKAT 2010 but revised and updated based on a newly found research paper about the same RCTs.

The Google search engine available on the EKAT website allows users to search structured abstracts in both EKAT 2010 and the EKAT Appendix 2011. The titles, target references, and the number of structured abstracts are shown below by report version.

Version/date	15-Jun-07	1-Apr-08	1-Jun-09	1-Jun-10	1-Oct-11
Title	Evidence Reports of Kampo Treatment, 2nd edition – Focusing on RCTs – Interim Report 2007	Evidence Reports of Kampo Treatment, 2nd edition – Focusing on RCTs – Interim Report 2007 ver, 1.1	Evidence Reports of Kampo Treatment, 2009 – 320 Randomized Controlled Trials (EKAT 2009)	Evidence Reports of Kampo Treatment, 2010 – 345 Randomized Controlled Trials (EKAT 2010)	Evidence Reports of Kampo Treatment, Appendix 2011 (EKAT Appendix 2011)
Year of publication of targeted references	1999 – 2005	1999 – 2005	1986 – Jun 2008	1986 – Jun 2009	Post- EKAT 2010 – Jun 2010
No. of references	104	116	385	416	16 [2)]
No. of structured abstracts (SA)	102	98	321 [1)]	346 [1)]	14
No. of excluded references	42	32	111	133	-

[1)] Including 1 meta-analysis

[2)] Including 2 additional references for structured abstracts already included in EKAT 2010

EKAT is published in Japanese and in English. An English version of this Appendix is likewise available on the JSOM website.

The Korean Oriental Medical Society EBM Special Committee published on July 15, 2011 the Korean version of EKAT 2010, "근거중심의 한방처방 : 임상 근거를 만들고, 전달하며, 사용하는 (Evidence-based Kampo Treatment: Generate, Transfer and Use Clinical Evidence)" This is available for sale at http://www.koonja.co.kr/shop/goods/goods_view.php?goodsno=13267.

Links to EKAT structured abstracts from the Cochrane Library (CENTRAL) are planned in the near future. (However, it is CENTRAL's policy not to create links to structured abstracts of papers that are already listed in CENTRAL.) In creating the links, a structured abstract will be given a link from the bibliographic information of only one major research paper for which that structured abstract was compiled. With regards structured abstracts compiled in the past based on multiple research papers, the key paper for which a link is to be created by CENTRAL will be shown in bold face. The abstractor's comment will undergo some minor alterations.

Third Phase (June 2009 -)
Task Force for Evidence Reports / Clinical Practice Guidelines (ER/CPG-TF)
Special Committee for Evidence-based Medicine (EBM)
The Japan Society for Oriental Medicine (JSOM)

Organization

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Ichiro ARAI	Subcommittee to Assess the Efficacy of Kampo Medicines, Committee on Kampo Formulations for Prescription, Japan Kampo Medicines Manufacturers Association
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Chairperson, Special Committee for EBM, Japan Society for Oriental Medicine (JSOM) / Trustee in charge of Special Committee for EBM, Japan Society for Oriental Medicine (JSOM):

Kiichiro TSUTANI	Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, University of Tokyo

（19 Jul. 2009 – 9 Jul. 2011）

Lists of Structured Abstracts

Note: Original English titles assigned by authors were used in this list and the structured abstracts. When references had no English titles, the Task Force translated the original Japanese titles into English ones (*).

Abbreviations: C: Cochrane Library (CENTRAL), I: *Igaku Chuo Zasshi* (*Japana Centra Revuo Medicana*, Ichushi), N : Database Offered by Nikkankyo (the Japan Kampo Medicines Manufacturers Association)

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
F05.9	To evaluate the efficacy of yokukansan (抑肝散) for postoperative delirium after cardiovascular surgery in the elderly.	yokukansan (抑肝散)	Takase Shinya. The efficacy of Yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 132−4 (in Japanese).	RCT-envelope	N	7
F20.9	To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.	yokukansan (抑肝散)	Miyaoka T, Furuya M, Yasuda H, et al. Yi-Gan San as adjunctive therapy for treatment-resistant schizophrenia: An open-label study. *Clinical Pharmacology* 2009; 32: 6–9.	RCT	N	8
G30.1	To investigate the efficacy and safety of yokukansan (抑肝散) as a common treatment for behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).	yokukansan (抑肝散)	Okahara K, Ishida Y, Hayashi Y, et al. Effects of Yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2010; 34: 532–6.	RCT	C	9
G30.1	To evaluate the efficacy of yokukansan (抑肝散) and risperidone in the treatment of behavioral and psychological symptoms of dementia (BPSD)	yokukansan (抑肝散)	Furuhashi Y. Comparative efficacy of risperidone versus Yokukansan (抑肝散) on behavioral and psychological symptoms of dementia in patients with Alzheimer's disease*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 120–1 (in Japanese).	RCT	N	10
J10.1	To evaluate the efficacy of coadministration of maoto (麻黄湯) and Shosaikoto (小柴胡湯) for the treatment of influenza A infection, in comparison to oseltamivir.	maoto (麻黄湯), Shosaikoto (小柴胡湯)	Yaegashi H. Efficacy of coadministration of maoto and shosaikoto, a Japanese traditional herbal medicine (Kampo medicine), for the treatment of influenza A infection, in comparison to oseltamivir. *Nihon Hokan Daitai Iryo Gakkaishi* (*Japanese Journal of Complementary and Alternative Medicine*). 2010; 7: 59–62 (in English with Japanese summary).	RCT	N	11
J11.1	To evaluate the efficacy of maoto (麻黄湯) against influenza A in adults.	maoto (麻黄湯)	Saita M, Naito T, Boku S, et al. The efficacy of Ma-Huang-Tang (maoto) against influenza. *Kampo to Meneki Arerugi* (*Kampo and Immuno-allergy*). 2010; 23: 17–26 (in Japanese with English abstract).	RCT	N	12
K11.7	To evaluate the effects of bakumondoto (麦門冬湯) on neuropeptide levels in human plasma and saliva.	bakumondoto (麦門冬湯)	Satoh Y, Itoh H, Takeyama M. Effects of bakumondoto on neuropeptide levels in human saliva and plasma. *Journal of Traditional Medicines* 2009; 26: 122–30.	RCT-cross over	I	13
K31.9	To evaluate the effects of daikenchuto (大建中湯) and orengedokuto (黄連解毒湯) on cardiac output (CO) and superior mesenteric artery (SMA) blood flow.	daikenchuto (大建中湯), orengedokuto (黄連解毒湯)	Takayama S, Seki T, Watanabe M, et al. The herbal medicine Daikenchuto increases blood flow in the superior mesenteric artery. *The Tohoku Journal of Experimental Medicine* 2009; 219: 319–30.	RCT-cross over	C&I	14
K52.9	To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for delayed diarrhea induced by irinotecan (CPT-11) in patients with metastatic gastric and colorectal cancer.	hangeshashinto (半夏瀉心湯)	Hibi S, Ina K, Furuta R, et al. Clinical effects of hange-shashin-to on combination therapy of S-1/irinotecan for patients with metastatic gastric and colorectal cancer*. Gan to Kagaku Ryoho (*Japanese Journal of Cancer Chemotherapy*) 2009; 36: 1485–8 (in Japanese with English abstract).	RCT-envelope	C&I	15

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
K91.9	To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal and colonic transit and bowel function in healthy humans.	daikenchuto (大建中湯)	Manabe N, Camilleri M, Rao A, et al. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2010; 298: G970–5.	DB-RCT	C	16
N50.8	To evaluate the efficacy of androgen replacement therapy (ART) combined with saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) for late-onset hypogonadism (LOH) syndrome.	saikokaryukotsuboreito (柴胡加竜骨牡蛎湯)	Sugimoto K, Shigehara K, Izumi K, et al. Effect of combination of Saiko-ka-ryukotsu-borei-to with androgen replacement therapy for LOH syndrome. *Nihon Sei Kino Gakkai Zasshi* (*Japanese Journal of Sexual Medicine*) 2009; 24: 349–53 (in Japanese).	RCT	I	17
R11.0	To evaluate the efficacy of rikkunshito (六君子湯) for anorexia and nausea/vomiting occurring after cancer chemotherapy for advanced esophageal cancer.	rikkunshito (六君子湯)	Seike J. Efficacy of rikkunshito for anorexia and nausea/vomiting caused by cancer chemotherapy*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 12–3 (in Japanese).	RCT	N	18
R68.8	To evaluate the efficacy of preoperative administration of hochuekkito (補中益気湯) for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.	hochuekkito (補中益気湯)	Iwagaki H, Saito S. Regulation of post-operative systemic inflammatory response syndrome (SIRS) by preoperative administration of hochuekkito (a Japanese herbal medicine). *Nihon Toyo Igaku Zqsshi* (*Kampo Medicine*) 2010; 61: 78–83 (in Japanese with English abstract).	RCT	I	19
S93.4	To evaluate the efficacy of a Western medicine and a Kampo medicine (jidabokuippo [治打撲一方]) for pain and swelling after a fresh and isolated anterior talofibular ligament (ATFL) grade III injury.	jidabokuippo (治打撲一方)	Takeda N. Conservative therapy for fresh lateral ligament injury of the ankle joint – Comparison of a Western medicine and a Kampo medicine for pain and swelling*. *Kampo to Rinsho* (*Journal of Kampo Medicine*) 2010; 1: 128–32 (in Japanese).	RCT	I	20

Revision of structured abstracts previously published in EKAT 2010

ICD-10	Research Question	Kampo Formula	References	Study Design	Source	Page No.
G30.1	To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease	yokukansan (抑肝散)	Monji A, Takita M, Samejima T, et al. Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2009; 33: 308-11.	RCT	N	21
			Monji A, Kanba S. Effectiveness of yokukansan (抑肝散) on BPSD in Alzheimer's disease — Results of a long-term antipsychotic combination trial at a department of neuropsychiatry in Kyushu*. *No 21* (*Brain 21*) 2009; 12: 446-51 (in Japanese).		I	
R05	To evaluate the efficacy of bakumondoto (麦門冬湯) on improvement in cough after lung cancer surgery	bakumondoto (麦門冬湯)	Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery. *Kampo to Meneki Arerugi* (*Kampo and Immuno-Allergy*) 2008; 22: 43-55 (in Japanese with English abstract).	RCT-envelope	I	22
			Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery — QOL analysis with 36-Item Short Form [SF-36] v2*. *Progress in Medicine* 2010; 30: 100-1 (in Japanese).		N	

Psychiatric/Behavioral Disorders

References

Takase Shinya. The efficacy of Yokukansan (抑肝散) on postoperative delirium after cardiovascular surgery in the elderly*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 132−4 (in Japanese).

1. Objectives

To evaluate the efficacy of yokukansan (抑肝散) for postoperative delirium after cardiovascular surgery in the elderly.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Department of Cardiovascular Surgery, Fukushima Medical University.

4. Participants

Thirty patients who underwent cardiovascular surgery since April 2009.

5. Intervention

Arm 1: administration of TSUMURA Yokukansan (抑肝散) Extract Granules 2.5 g t.i.d. from 5 days prior to surgery until the day of discharge except for the day of surgery (n=15).
Arm 2: no administration (n=15).

6. Main outcome measures

Each item on the 10-item Delirium Rating Scale-J (DRS-J) (orientation, hallucination, delusions, agitation, motor restraints, perceptual disturbances, physical disorders, sleep-wake cycle disturbance, lability of mood, fluctuation of symptom severity). Assessment by physicians of 10 items of the DRS-J at 5 days prior to surgery, and 3 and 10 days after surgery. Assessment by nurses of 6 items at 5 days prior to surgery and 1–5, 7, 10, 12, 14, and 16 days after surgery.

7. Main results

In the assessments by physicians, there were significant between-arm differences in orientation (P=0.0033), delusion (P=0.021), agitation (P=0.0011), and lability of mood (P=0.0044). In the assessments by nurses, there were significant between-arm differences in hallucination (P=0.0383), agitation (P=0.0049), and lability of mood (P=0.0364). Both physicians (P=0.0331) and nurses (P=0.0245) found that the overall score had improved significantly after treatment (Arm 1).

8. Conclusions

Yokukansan is effective for preventing delirium after cardiovascular surgery in elderly patients.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No hypokalemia, which often occurs after cardiovascular surgery, was observed.

11. Abstractor's comments

This is an innovative clinical trial evaluating the efficacy of yokukansan for delirium after cardiovascular surgery in the elderly. It is meaningful that they used yokukansan to solve an actual clinical problem such as post-operative delirium and demonstrated its effectiveness. However, this article is a summary of conference presentation, and regrettably fails to describe the methods and results precisely. Details of the study including the number of withdrawals, the degree of improvement for items such as "orientation" and "delusion" in comparison to the control group, and the method for calculating overall score, are awaited in a journal article, which has not yet been published. This interesting clinical study provides a helpful perspective for a future large-scale study assessing the efficacy of yokukansan for preventing post-operative delirium in the elderly.

12. Abstractor and date

Goto H, 25 December 2010.

Psychiatric/Behavioral Disorders

References

Miyaoka T, Furuya M, Yasuda H, et al. Yi-Gan San as adjunctive therapy for treatment-resistant schizophrenia: An open-label study. *Clinical Pharmacology* 2009; 32: 6–9.

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) for treatment-resistant schizophrenia.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Psychiatry, Shimane University School of Medicine.

4. Participants

Patients diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) who met treatment-resistance criteria as follows:

a) no satisfactory response to antipsychotic drugs from at least 2 different classes, in a dose equivalent to at least 1000 mg/d of chlorpromazine for at least 6 weeks during the course of illness;

b) no period of good functioning within the preceding 2 years;

c) positive and negative syndrome scale (PANSS) scores in the 70th percentile or higher, based on normative data for patients with chronic schizophrenia.

5. Intervention

The study was brief (4 weeks) and had an open-label design.

Arm 1: administration of Yokukansan (抑肝散) 6.7 ±2.5 g (range, 2.5–7.5 g)/day (n=34).

Arm 2: no administration of Yokukansan (抑肝散) (n=25).

All patients were taking conventional and/or atypical antipsychotic medications, including olanzapine, risperidone, quetiapine, aripiprazole, perospirone, haloperidol, levomepromazine, and zotepine.

6. Main outcome measures

PANSS and drug-induced extrapyramidal symptom scale (DIEPSS) were assessed at baseline, and after 2 and 4 weeks of treatment.

7. Main results

In Arm 1, treatment with Yokukansan significantly reduced the PANSS positive symptoms subscale score of 27.7±6.1 at baseline by 68.2% at 2 weeks (means score 18.9±5.0) (P<0.001) and 43.0% at 4 weeks (mean score, 11.9±3.7) (P<0.001), the PANSS negative symptom subscale score of 30.4±5.8 at baseline by 73.7% at 2 weeks (mean score, 22.4±4.3) (P<0.001) and 59.9% at 4 weeks (mean score, 18.2±2.2) (P<0.001), and the PANSS general psychopathology subscale score of 65.1±5.4 at baseline by 70.5% (mean score, 45.9±9.0) (P<0.001) at 2 weeks and 60.8% (means score, 39.6±6.9) (P<0.001) at 4 weeks. In the control group, each PANSS subscale remained unchanged. There was no significant difference in the DIEPSS scores in both groups.

8. Conclusions

In this pilot study, statistically significant improvement in clinical assessment scale was observed after yokukansan treatment, suggesting that yokukansan has efficacy for treatment-resistant schizophrenia.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

DIEPSS corresponds to the safety assessment, and no serious adverse effects of yokukansan were reported. A few mild and transient adverse events included 2 cases of nausea and 1 case of tiredness.

11. Abstractor's comments

This RCT was designed to evaluate the efficacy of yokukansan for schizophrenia, as it has been shown to be effective in treating psychiatric disorders such as dementia. The idea is great and the result is clinically significant. As the authors discuss, the absence of blinding may have introduced bias into the outcome assessment. The total number of the participants of the two arms is 59. However, the Figure 1 legend states that 54 completed a 4-week trial, making unclear the number of subjects who dropped out. Because of the small sample size, the number of subjects used as denominator for analyses is a concern. More precise design for the main trial is anticipated.

12. Abstractor and date

Tsuruoka K, 2 January 2011.

Nervous System Diseases (including Alzheimer's Disease)

References

Okahara K, Ishida Y, Hayashi Y, et al. Effects of Yokukansan on behavioral and psychological symptoms of dementia in regular treatment for Alzheimer's disease. *Progress in Neuro Psychopharmacology & Biological Psychiatry* 2010; 34: 532–6.

1. Objectives

To investigate the efficacy and safety of yokukansan (抑肝散) as a common treatment for behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease (AD).

2. Design

Randomized controlled trial (RCT).

3. Setting

Hospitals and Clinics in Miyazaki and Kagoshima prefecture, 12 institutions.

4. Participants

Sixty-three outpatients were registered from July 2006 to December 2008 and met the following inclusion criteria: 1) have dementia and a diagnosis of Alzheimer's disease (including mixed-type dementia), 2) show at least one symptom score ≥4 in the Neuropsychiatric Inventory (NPI) subscales, 3) aged ≤85 years, 4) taking donepezil hydrochloride for at least 4 weeks.

5. Intervention

Arm 1: administration of TSUMURA Yokukansan (抑肝散) Extract Granules, 2.5 g t.i.d. for 4 weeks (n=30).

Arm 2: no administration (n=33).

6. Main outcome measures

Evaluations of BPSD using the NPI subscales (delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor activity), cognitive function by the Mini-Mental State Examination (MMSE), activities of daily living (ADL) by the Disability Assessment of Dementia (DAD), burden of caregivers by the Zarit Burden Interview, caregiver's depression by the Self-rating Depression Scale (SDS) at the start and at 4 weeks of the study.

7. Main results

One patient in arm 1 and one patient in arm 2 withdrew, and the efficacy analysis set included 29 patients in arm 1 and 32 patients in arm 2. Inter-group comparison revealed significantly more improvement in arm 1 compared with arm 2 in the total NPI score after 4 weeks of treatment (P<0.05). On analysis of individual NPI subscale scores, significant improvement was observed for agitation and irritability in arm 1 compared to arm 2 (P<0.05). Intra-group comparison of values at the start and at 4 weeks of treatment identified a significant improvement in the NPI total score in arm 1 (P<0.05). Analysis of each NPI subscale scores at baseline and after 4 weeks of treatment demonstrated significant improvement in delusions, agitation, dysphoria, anxiety, apathy, or irritability in arm 1 (P<0.05), and in apathy in arm 2 (P<0.05). Inter-group and intra-group comparisons found no changes in MMSE, DAD, Zarit Burden Interviews, or SDS.

8. Conclusions

Yokukansan significantly accelerates improvement in BPSD in patients with Alzheimer's disease treated with donepezil.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None of the patients had any adverse reactions to yokukansan such as decreased serum potassium or edema.

11. Abstractor's comments

This is a clinical trial to determine the efficacy of yokukansan for dementia in patients with Alzheimer's disease treated with donepezil by evaluating its effect on behavioral and psychological symptoms. The result of the clinical trial can be applied immediately to daily practice. Despite improvement in NPI scores, scores reflecting the burden of caregivers were not improved. To assess this effect, further studies with larger sample size and longer study period would be necessary. However, as no drugs effective for peripheral symptoms of dementia are presently available, demonstration of the efficacy of yokukansan is a great achievement.

12. Abstractor and date

Goto H, 27 December 2010.

Nervous System Diseases (including Alzheimer's Disease)

References

Furuhashi Y. Comparative efficacy of risperidone versus Yokukansan (抑肝散*) on behavioral and psychological symptoms of dementia in patients with Alzheimer's disease. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 120–1 (in Japanese).

1. Objectives

To evaluate the efficacy of yokukansan (抑肝散) and risperidone in the treatment of behavioral and psychological symptoms of dementia (BPSD)

2. Design

Randomized controlled trial (RCT).

3. Setting

Asahi hospital, units of psychiatry, psychosomatic internal medicine, and geriatric psychiatry.

4. Participants

Twenty patients admitted to the hospital between January 2008 and January 2009 who met Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) or International Classification of Diseases (ICD) criteria for Alzheimer's disease.

5. Intervention

Arm 1: yokukansan (抑肝散) (manufacturer not specified) 7.5 g/day for 4 weeks (n=10
Arm 2: risperidone 0.5 mg/day for 4 weeks (n=10

6. Main outcome measures

Neuropsychiatric Inventory (NPI; for psychological symptoms) and the Cohen-Mansfield Agitation Inventory (CMAI; for behavioral symptoms) were used for evaluation.

7. Main results

Significant improvements in NPI scores and CMAI scores were observed in both the risperidone arm and yokukansan arm (P<0.01).

8. Conclusions

Both yokukansan and risperidone have a similar effect on BPSD.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Sedation, malaise, drowsiness, and constipation were reported in arm 2, but no adverse events were reported in arm 1.

11. Abstractor's comments

This paper discusses the effect of yokukansan on the peripheral symptoms of Alzheimer's disease. More and more patients with dementia are being treated with yokukansan, and this paper reflects this recent trend. From the viewpoint of Kampo medicine, yokukansan is expected to reduce anger. Most anticipated is the efficacy of yokukansan on peripheral symptoms, especially on agitation, which should alleviate the burden on caregivers. Though no data were shown, this paper stated that yokukansan significantly improved CMAI scores for aggressive behaviors such as beating, kicking, grabbing, scratching, and breaking, and unaggressive behaviors such as repeating the same action over and over and asking questions continuously. These seem to be the exact effects of yokukansan. A precise report with details is awaited.

12. Abstractor and date

Nakata H, 12 January 201

Respiratory Diseases (including Influenza and Rhinitis)

References

Yaegashi H. Efficacy of coadministration of maoto and shosaikoto, a Japanese traditional herbal medicine (Kampo medicine), for the treatment of influenza A infection, in comparison to oseltamivir. *Nihon Hokan Daitai Iryo Gakkaishi* (*Japanese Journal of Complementary and Alternative Medicine*). 2010; 7: 59–62 (in English with Japanese summary).

1. Objectives

To evaluate the efficacy of co administration of maoto (麻黄湯) and Shosaikoto (小柴胡湯) for the treatment of influenza A infection, in comparison to oseltamivir.

2. Design

Randomized controlled trial (RCT).

3. Setting

A single clinic.

4. Participants

Fourteen outpatients (18 years or older) who presented within 48 hours after onset of fever (body temperature above 37.5 °C) with influenza-like symptoms (upper respiratory tract symptoms or systemic symptoms) and tested positive for influenza A antigen from December 2007 to March 2008.

5. Intervention

Arm 1: administration of TSUMURA Maoto (麻黄湯) Extract Granules 2.5 g t.i.d. + TSUMURA Shosaikoto (小柴胡湯) Extract Granules 2.5 g t.i.d. for 3 days (n=6).
Arm 2: administration of oseltamivir 75 mg b.i.d. for 5 days (n=8).

6. Main outcome measures

Duration of fever, highest body temperature, and number of doses of antipyretics and cough medicines.

7. Main results

There was no significant between-arm difference in duration of fever after onset (2.8±0.8 [mean±SD] days in arm 1 and 2.9±0.7 days in arm 2), duration of fever after treatment (2.9±0.7 days in arm 1 and 2.0±0.6 days in arm 2), the highest body temperature (39.0±0.7°C in arm 1 and 38.8±0.5°C in arm 2), and the number of doses of antipyretics and cough medicines administered.

8. Conclusions

The efficacy of maoto plus shosaikoto for treating influenza A in adults was comparable to that of oseltamivir.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

No adverse effects were observed in both arms.

11. Abstractor's comments

This paper reports a randomized controlled trial of maoto plus shosaikoto for treatment of influenza A. The effect of maoto combined with shosaikoto was comparable to that of oseltamivir. To strengthen the evidence, the efficacy needs to be confirmed in a study with a larger sample size. However, coadministration of maoto and shosaikoto is not logical from the viewpoint of Kampo medicine. Patients who did not respond to maoto should be treated with daiseiryuto (大青竜湯), keishinieppiichito (桂枝二越婢一湯), saikatsugekito (柴葛解肌湯), or saikokeishito (柴胡桂枝湯 according their excess or deficiency (虚実) pattern, and not with maoto plus shosaikoto.

12. Abstractor and date

Okabe T, 24 December 2010.

Respiratory Diseases (including Influenza and Rhinitis)

References

Saita M, Naito T, Boku S, et al. The efficacy of Ma-Huang-Tang (maoto) against influenza. *Kampo to Meneki Arerugi* (*Kampo and Immuno-allergy*). 2010; 23: 17–26 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of maoto (麻黄湯) against influenza A in adults.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of General Medicine, Juntendo University School of Medicine.

4. Participants

Forty-five patients (20 years or older) visiting the hospital between November 2008 and March 2009 and testing positive for type A influenza antibody using a rapid diagnosis kit.

5. Intervention

Subjects were randomized to either of two arms, using Microsoft Excel.

Arm 1: TSUMURA Maoto (麻黄湯) Extract Granules (n=22, 9 of whom were concomitantly treated with oseltamivir).

Arm 2: oseltamivir or zanamivir (n=23, 13 of whom were treated with oseltamivir and 6 of whom were treated with zanamivir).

6. Main outcome measures

Symptoms (pyrexia [period from administration of drugs to afebrility], arthralgia, myalgia, headache, cough, and malaise) scored on a 5-point scale. Scores recorded daily for 5 days and sent by mail by each participant.

7. Main results

Patients who provided complete data for analysis (18 patients in arm 1 and 19 patients in arm 2) were included. Of these 37 patients, 7 patients in arm 1 and 11 patients in arm 2 had received influenza vaccination. At the time of the allocation, there were no significant differences in age (arm 1, 31.1±9.77 years; arm 2, 33.6±13.1 years), the presence or absence of fever at the first visit, and duration of fever. During the period from administration of drugs to afebrility, there was no between-arm difference in duration of fever. Although the time to improvement of myalgia tended to be faster in arm 1, the time to disappearance of other symptoms was similar in both arms.

8. Conclusions

Maoto and anti-influenza agents have the same antipyretic effects in patients with influenza.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

The topic of this article was presented at a meeting. It is interesting that the authors found no significant differences in the effects of maoto and other agents on the clinical course of influenza infection. However, there is a source of bias in the use of anti-influenza agents, and the finding of no significant differences should be interpreted with caution. Their conclusion is based on a comparison of the efficacy of maoto and anti-influenza drugs, but this comparison is not assessable using this study design.

12. Abstractor and date

Fujisawa M, 14 January 2011.

Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References
Satoh Y, Itoh H, Takeyama M. Effects of bakumondoto on neuropeptide levels in human saliva and plasma. *Journal of Traditional Medicines* 2009; 26: 122–30.

1. Objectives
To evaluate the effects of bakumondoto (麦門冬湯) on neuropeptide levels in human plasma and saliva.

2. Design
Randomized cross-over controlled trial (RCT-cross over).

3. Setting
Oita University Hospital.

4. Participants
Five non-smoking males, aged 25–30 years.

5. Intervention
Arm 1: a single administration of TSUMURA Bakumondoto (麦門冬湯) Extract Granules 18 g.
Arm 2: placebo (lactose + maltose).
Each subject was administered these drugs with an interval of four weeks.

6. Main outcome measures
Substance P, vasoactive intestinal polypeptide (VIP), somatostatin, and calcitonin-gene related peptide (CGRP) levels in plasma and saliva.

7. Main results
Treatment in arm 1 significantly increased saliva levels of substance P level at 40 min after administration of bakumondoto (mean±SD of 37.8±14.7 pg/mL *vs* 23.5±10.2 pg/mL in arm 2; *P*=0.0317) and CGRP at 90 min after administration (65.5±34.4 pg/mL *vs* 24.8±4.5 pg/mL in arm 2; *P*=0.0079), but not VIP, which remained unchanged. Treatment in arm 1 also significantly increased plasma levels of substance P at 90 min after administration (34.1±14.0 pg/mL *vs* 23.3±2.8 pg/mL in arm 2; *P*=0.0127), but not of CGRP and VIP. Saliva volume was increased by 37%, 26%, and 33% at 20, 40, and 60 min in arm 1, but not in arm 2. Saliva secretion was correlated with saliva level of substance P (r=0.66).

8. Conclusions
Bakumondoto increases substance P and CGRP levels in human saliva. An increase in saliva secretion by bakumondoto is partially attributable to increases in these neuropeptides.

9. From Kampo medicine perspective
None.

10. Safety assessment in the article
None.

11. Abstractor's comments
This study is interesting because it evaluates the increases in substance P and CGRP secretion as a contributor to the stimulatory effect of bakumondoto on salivary secretion in a cross-over study. Considering the results of this study, which implicate neuropeptides in the mechanism of action of bakumondoto, and the reported involvement of substance P in the effect of hangekobokuto (半夏厚朴湯) on improvement of swallowing disorder, further elucidation of the pharmacological action of bakumondoto is awaited.

12. Abstractor and date
Okabe T, 27 December 2010.

Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Takayama S, Seki T, Watanabe M, et al. The herbal medicine Daikenchuto increases blood flow in the superior mesenteric artery. *The Tohoku Journal of Experimental Medicine* 2009; 219: 319–30.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) and orengedokuto (黄連解毒湯) on cardiac output (CO) and superior mesenteric artery (SMA) blood flow.

2. Design

Randomized cross-over controlled trial (RCT-cross over).

3. Setting

Single facility (Tohoku University Hospital).

4. Participants

Fourteen healthy adults (25–44 years old) without cardiac disease.

5. Intervention

Arm 1: distilled water (50 mL, 37°C).
Arm 2: TSUMURA Daikenchuto (大建中湯) Extract Granules5.0 g.
Arm 3: TSUMURA Orengedokuto (黄連解毒湯) Extract Granules 2.5 g.

6. Main outcome measures

Hemodynamic parameters including CO, blood pressure, heart rate, and SMA blood flow, measured by impedance cardiography (ICG) before and at 5, 10, 15, 20, 30, 45, 60, 75, and 90 min after administration of distilled water, daikenchuto, and orengedokuto.

7. Main results

Although neither daikenchuto nor orengedokuto affected CO, daikenchuto significantly increased SMA blood flow compared with distilled water or orengedokuto (P<0.05). Five grams of daikenchuto significantly increased SMA blood flow between 5 min (P<0.01) and 90 min after administration, with a peak reached at 20 min.

8. Conclusions

Daikenchuto increases SMA blood flow without changing CO in healthy people.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study used a physiological approach to verify the blood flow-increasing effect of daikenchuto, which is used for *kansho* (寒証, cold pattern/syndrome), and the blood flow-suppressing effect of orengedokuto, which is used for *netsusho* (熱証, heat pattern/syndrome). Daikenchuto is well-known for its gastrointestinal prokinetic effect and is clinically applied to subileus cases regardless of *sho* (証, pattern/syndrome) with certain efficacy. This study revealed that daikenchuto increases SMA blood flow, possibly providing practicing clinicians with valuable findings. However, as this study was performed in healthy people, it not certain that the outcome of daikenchuto therapy is the same in patients in the ileus state or with *hie* (冷え, a feeling of coldness) in the pelvis. Based on the results of this study in healthy adults, future studies are expected to identify the mechanisms of action (probably more than one) of these Kampo medicines (daikenchuto in subileus cases with *kansho* [寒証, cold pattern/syndrome] and orengedokuto in hypertension and insomnia cases with *netsusho* [熱証, heat pattern/syndrome]) using the same study protocol.

12. Abstractor and date

Ushiroyama T, 16 January 2011.

Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Hibi S, Ina K, Furuta R, et al. Clinical effects of hange-shashin-to on combination therapy of S-1/irinotecan for patients with metastatic gastric and colorectal cancer*. Gan to Kagaku Ryoho (*Japanese Journal of Cancer Chemotherapy*) 2009; 36: 1485–8 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of hangeshashinto (半夏瀉心湯) for delayed diarrhea induced by irinotecan (CPT-11) in patients with metastatic gastric and colorectal cancer.

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope).

3. Setting

Single facility.

4. Participants

Twenty patients with inoperable advanced recurrent gastric cancer or colorectal cancer (12 males and 8 females).

5. Intervention

Patients received a course of chemotherapy consisting of 2 weeks on and 2 weeks off oral S-1 (tegafur/gimeracil/oteracil potassium) at 80–120 mg according to body surface area and intravenous irinotecan (CPT-11) at 100–125 mg once every 2 weeks.

Arm 1: Hangeshashinto (半夏瀉心湯) extract 7.5 g/day for 3 days starting on the day of administration of irinotecan (CPT-11) (n=10).

Arm 2: no administration of hangeshashinto (半夏瀉心湯) extract (n=10).

6. Main outcome measures

Anti-tumor effect (RECIST criteria), adverse events (Common Terminology Criteria for Adverse Events v3.0), and quality of life (QOL score developed by Kurihara et al.) evaluated on days 1, 15, and 29.

7. Main results

There was no significant difference in anti-tumor effect between arms. Chemotherapy-associated adverse events were more common in arm 2 than in arm 1 (significance of difference not tested). A decrease in QOL score from day 1 to day 15 was larger in more patients in arm 2 than in arm 1. Overall QOL score was decreased by 15 points or more in 1 patient in arm 1, compared with 4 patients in arm 2, with the mean±standard deviation significantly changed from 79±19 and 87±13 on day 1 to 77±21and 75±23 on day 15 in arm 1 and arm 2, respectively (P<0.05). In particular, QOL in the "social" domain decreased 2 points or more in 7 of 10 patients in arm 2 and 0 of 10 patients in arm 1.

8. Conclusions

Hangeshashinto (半夏瀉心湯) is a useful supportive therapy from the viewpoint of QOL in patients treated for advanced gastric and colorectal cancer with S-1/irinotecan (CPT-11) combination therapy.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

Post-marketing surveillance identified gastrointestinal symptoms such as nausea/vomiting (52.5%), anorexia (48.1%), and abdominal pain (12.2%) as frequent adverse drug reactions of CPT-11, besides diarrhea (43%, serious in 10.2% of cases). Hangeshashinto has well known efficacy not only for diarrhea, as reported by Kamataki et al. (1994), but also for nausea/vomiting, anorexia, and epigastric pain. This study demonstrated that hangeshashinto improves QOL. But the study had the following problems: (1) the rationale for the 3-day hangeshashinto administration period after administration of CPT-11 is not indicated. Although the authors seem to assume that the hangeshashinto-*sho* (証, pattern/syndrome) induced by CPT-11 disappears in 3 days, delayed diarrhea attributable to intestinal mucosal injury by an active metabolite (SN-38) 24 hr after administration, for example, does not disappear in 3 days, warranting consideration of duration of administration in the future; (2) hangeshashinto is effective in only some cases. As QOL score was decreased by 15 points or more in 4 of 10 patients in arm 2 in this study, only these 4 patients are likely to have exhibited hangeshashinto-*sho* (証, pattern/syndrome). It is recommended that patients be enrolled in the study from the second cycle onward after determining the presence or absence of hangeshashinto-*sho* (証, pattern/syndrome) and the duration of the *sho* (証, pattern/syndrome), based on the response to the first cycle of CPT-11.

12. Abstractor and date

Hoshino E, 15 January 2011.

Gastrointestinal, Hepato-Biliary-Pancreatic Diseases

References

Manabe N, Camilleri M, Rao A, et al. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2010; 298: G970–5.

1. Objectives

To evaluate the effects of daikenchuto (大建中湯) on gastrointestinal and colonic transit and bowel function in healthy humans.

2. Design

Double-blind randomized controlled trial (DB-RCT).

3. Setting

Mayo Clinic, US.

4. Participants

Sixty healthy adults (18–65 years old) without gastrointestinal disorders recruited by advertisement. Those with a history of allergic reactions to egg, ginseng, ginger, and Sichuan pepper were excluded.

5. Intervention

Treatment was administered t.i.d. immediately before meals for 5 consecutive days. Participants and study personnel were blinded (double-blind) to treatment assignment.
Arm 1: daikenchuto (大建中湯) (manufacturer, not specified) 2.5 g t.i.d. (n=19).
Arm 2: daikenchuto (大建中湯) (manufacturer, not specified) 5 g t.i.d. (n=20).
Arm 3: identical placebo (n=21).

6. Main outcome measures

Primary outcomes: gastric emptying half-time (GE $t_{1/2}$) measured by scintigraphy; colonic geometric center at 24 h (GC24); ascending colon emptying half-time (AC emptying $t_{1/2}$).
Secondary outcomes: colonic geometric center at 4 h and 48 h (GC4, GC48); colonic filling at 6 h; stool frequency and consistency (self-assessed using the Bristol Stool Form Scale).

7. Main results

There was a difference in colonic filling at 6 h between both daikenchuto groups and the placebo group (P=0.04). Pair-wise comparisons between Arm 1 and Arm 3 and between Arm 2 and Arm 3 showed no significant differences. Daikenchuto 7.5 g/day tended to accelerate ascending colon emptying half-time (P=0.07) and daikenchuto at both doses tended to raise GC24 (P=0.63). However, daikenchuto had no meaningful effects on gastric emptying half-time (P=0.45), stool frequency (P=0.80), or stool consistency (P=0.33).

8. Conclusions

Daikenchuto accelerated colonic filling at 6 h and ascending colon emptying half-time in healthy humans, suggesting that it promotes small bowel motility and hastens ascending colon transit.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

One subject receiving daikenchuto 7.5 g/day had increased creatine phosphokinase (CPK) 1 month after receiving the study medication, which was discovered when the subject presented to the emergency department for muscle pain. With no evidence of myopathy, CPK level returned to normal at 4 months without intervention.

11. Abstractor's comments

This is a well-designed DB-RCT. Regrettably, no statistically significant difference was detected, which may be partly because the study population was healthy volunteers, considering the characteristics of Kampo medicine. The results of future RCTs being planned by the authors in patients with gastrointestinal disorders, including irritable bowel syndrome and constipation, are expected.

12. Abstractor and date

Tsuruoka K, 7 January 2011.

Genitourinary Tract Disorders (including Climacteric Disorders)

References

Sugimoto K , S higehara K , I zumi K , e t a l. E ffect of c ombination of S aiko-ka-ryukotsu-borei-to w ith androgen r eplacement t herapy for L OH s yndrome. *Nihon Sei Kino Gakkai Zasshi* (*Japanese Journal of Sexual Medicine*) 2009; 24: 349–53 (in Japanese).

1. Objectives

To e valuate t he efficacy of a ndrogen r eplacement t herapy (ART) combined with s aikokaryukotsuboreito (柴胡加竜骨牡蛎湯) for late-onset hypogonadism (LOH) syndrome.

2. Design

Randomized controlled trial (RCT).

3. Setting

Two facilities (Kanazawa University Hospital and Ishikawa Prefectural Central Hospital).

4. Participants

Thirteen s ubjects w ho w ere diagnosed w ith LOH s yndrome a t t he a bove f acilities a nd d esired t o r eceive treatment.

5. Intervention

Arm 1: intramuscular testosterone enanthate 250 mg/3–4 weeks for 12 weeks (n=7).

Arm 2: intramuscular t estosterone e nanthate 2 50 mg/3–4 w eeks + a dministration of saikokaryukotsuboreito (柴胡加竜骨牡蛎湯) (manufacturer, not specified) 2.5 g t.i.d. immediately before meals for 12 weeks (n=6).

6. Main outcome measures

1) A ging M ales Symptoms (AMS) r ating scale, 2) S elf-rating Depression Scale (S DS), 3) s elf-rating Internal I ndex of Erectile F unction-5 (IIEF-5), and 4) b lood t estosterone c oncentration, e valuated a t t he start of treatment and after 12 weeks of treatment.

7. Main results

Combination treatment tended to improve AMS, SDS, and IIEF-5 scores compared w ith ART alone. Decreases i n b lood t otal t estosterone a nd free testosterone concentrations w ere g reater a fter ART al one than after combination treatment.

8. Conclusions

Saikokaryukotsuboreito plus ART for late-onset hypogonadism (LOH) syndrome improves psychiatric and physical symptoms and alleviates ART-induced gonadal function depression.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Blood biochemistry identified no serious adverse events.

11. Abstractor's comments

This s tudy focused on t he central n ervous s ystem depressant a ctivity of s aikokaryukotsuboreito a s a *saiko-zai* (柴胡剤, saiko formulation) or r yukotsu (竜骨)- and b orei (牡蛎)-containing K ampo medicine, and c ompared t he ef fect o f i ts co mbination w ith a ndrogen r eplacement t herapy to t hat of androgen replacement therapy a lone, using major r ating s cales c linically used t o evaluate late-onset hypogonadism (LOH) syndrome. Its attempt to find out the favorable effects of Kampo medicine (when in combination) is worthy of appreciation. This study, however, fails to determine *sho* (証, pattern/syndrome) of cases with appreciable de pression a nd unidentified c omplaints, w hich a re c ommon in middle-aged and e lderly m en, and i ts finding t hat s aikokaryukotsuboreito i s more e ffective t han A RT a lone for anxiety a nd depressive symptoms in cases of *ki-tai* (気滞, qi stagnation) and *hi-ki-kyo* (脾気虚, spleen qi deficiency) is consistent with conventional clinical wisdom and practice a nd i s not new. Furthermore, the sample size o f 6–7 subjects per group was extremely small. It is hoped that similar studies will be performed with many more "saiko-*sho* (証, pattern/syndrome)" and "ryukotsuborei- *sho* (証, pattern/syndrome)" cases, w hich c an be diagnosed b y c linicians r elatively early a nd without un certainty to establish t he g uidelines for not on ly combination therapy with ART b ut also for selecting usage according t o *sho* (証, pattern/syndrome). Evaluation o f whether a hi gh percentage of patients w ith LOH syndrome is indicated f or saikokaryukotsuboreito is also expected.

12. Abstractor and date

Ushiroyama T, 15 January 2011.

Symptoms and Signs

References

Seike J. Efficacy of rikkunshito for anorexia and nausea/vomiting caused by cancer chemotherapy*. *Kampo Igaku* (*Science of Kampo Medicine*) 2010; 34: 12–3 (in Japanese).

1. Objectives

To evaluate the efficacy of rikkunshito (六君子湯) for anorexia and nausea/vomiting occurring after cancer chemotherapy for advanced esophageal cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Department of Thoracic, Endocrine Surgery and Oncology, Tokushima University Hospital.

4. Participants

Eighteen patients to receive DFP (docetaxel+5-FU+cisplatin) therapy for primary advanced esophageal cancer (mainly stage II–III).

5. Intervention

Two-week administration.
Arm 1: TSUMURA Rikkunshito (六君子湯) Extract Granules 2.5 g t.i.d. (n=8).
Arm 2: no administration (n=10).

6. Main outcome measures

Grade of anorexia and nausea/vomiting (Common Terminology Criteria for Adverse Events [CTC-AE] ver. 3.0), QOL score (the QOLQuestionnaire for Cancer Patients Treated with Anticancer Drugs [QOL-ACD]-based original questionnaire), blood ghrelin level.

7. Main results

The analysis population consisted of 18 subjects. Anorexia, nausea, and vomiting occurred as adverse drug reactions by 14 days after the start of chemotherapy in 3 (37.5%), 3 (37.5%), and 1 (12.5%) subject, respectively, in arm 1, and 7 (70%), 8 (80%) and 4 (40%) subjects, respectively, in arm 2. The change in mean vomiting score was 0 in both arms by day 8, but was 0.13 in arm 1 and 0.90 in arm 2 on day 14. Nausea score increased from day 8 and day 5 to 0.50 and 1.80 on day 14 in arm 1 and arm 2, respectively, showing significant difference on day 14 (P=0.034). Likewise, anorexia score reached 0.75 in arm 1 and 1.70 in arm 2 on day 14, showing a tendency toward lower score after rikkunshito administration. Rikkunshito also prevented significant suppression of depressed mood and decreased activities of daily living (P=0.027). Blood ghrelin level could not be evaluated because of large individual variability.

8. Conclusions

Rikkunshito significantly suppresses anorexia and nausea/vomiting caused by chemotherapy (DFP therapy) for advanced esophageal cancer, and thereby prevents significant decline in QOL.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study is highly valued because it demonstrated by RCT that rikkunshito significantly relieves nausea and prevents QOL score from decreasing after chemotherapy. However, this 14-day study with a small sample size was too short, warranting longer-term observation. Since basic research has demonstrated that rikkunshito improves cisplatin-caused anorexia by a ghrelin-mediated mechanism, further clinical studies with high level investigations, including analysis of blood ghrelin level, which could not be evaluated in this study, are expected.

12. Abstractor and date

Motoo Y, 30 December 2010.

Symptoms and Signs

References

Iwagaki H, Saito S. Regulation of post-operative systemic inflammatory response syndrome (SIRS) by preoperative administration of hochuekkito (a Japanese herbal medicine). *Nihon Toyo Igaku Zqsshi* (*Kampo Medicine*) 2010; 61: 78–83 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of preoperative administration of hochuekkito (補中益気湯) for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.

2. Design

Randomized controlled trial (RCT).

3. Setting

Okayama University Hospital and 8 related facilities.

4. Participants

Fifty-one patients undergoing laparotomy for advanced gastric/colon cancer in the period between February and December 2004.

5. Intervention

Medication taken for 7 consecutive days preoperatively to the day before surgery.
Arm 1: hochuekkito (補中益気湯) extract granules (manufacturer not indicated) 2.5 g t.i.d. (n=24).
Arm 2: no administration (n=27).

6. Main outcome measures

Serum cortisol level and soluble interleukin (IL)-2 receptor (sIL-2R) level immediately before and at 1 day after the operation; white blood cell (WBC) count and differential WBC count before and 1 and 7 days after the operation; C-reactive protein (CRP) level before and 1, 3, and 7 days after the operation; body temperature/pulse rate from the day before to 14 days after the operation; use of antibiotics until 14 days after the operation.

7. Main results

The analysis population consisted of 48 patients (after 2 and 1 patient dropped out in arm 1 and arm 2, respectively). There was no significant between-arm difference in preoperative serum cortisol level, but a tendency toward lower preoperative sIL-2R level in the hochuekkito group (P=0.08). The percent decline in cortisol level from preoperative baseline to postoperative day 1 value was significantly greater in arm 1 than in arm 2 (P=0.04), while there was no significant between-arm difference in the decline in sIL-2R level, WBC count, differential WBC count, or CRP level before and 1 and 7 days after the operation. The pre- to postoperative declines in mean body temperature and mean pulse rate were significantly greater in arm 1 (P=0.0002 and P=0.03, respectively). Fewer patients used second-line antibiotics postoperatively in the hochuekkito group than in the control group (P=0.05).

8. Conclusions

Preoperative administration of hochuekkito significantly suppresses the postoperative inflammatory response to surgical wounding.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

None.

11. Abstractor's comments

This study is significant because it demonstrates by RCT that preoperative 1-week administration of hochuekkito significantly suppresses postoperative SIRS, while focusing on the characteristics of Kampo medicine for treating *mibyou* (未病, subclinical state). The use of antibiotics, mentioned in the last section of the results, was said to be "significantly different between arms" even though P=0.05. The criterion for significance, indicated in the text, was P <0.05. Preoperative administration of hochuekkito reduced postoperative complications and duration of hospitalization, which is medically and economically beneficial. Furthermore, administration of hochuekkito may raise the awareness of patients and prepare them for surgery.

12. Abstractor and date

MotooY, 30 December 2010.

Extrinsic Injuries/Diseases

References

Takeda N. Conservative therapy for fresh lateral ligament injury of the ankle joint – Comparison of a Western medicine and a Kampo medicine for pain and swelling*. *Kampo to Rinsho* (*Journal of Kampo Medicine*) 2010; 1: 128–32 (in Japanese).

1. Objectives

To evaluate the efficacy of a Western medicine and a Kampo medicine (jidabokuippo [治打撲一方]) for pain and swelling after a fresh and isolated anterior talofibular ligament (ATFL) grade III injury.

2. Design

Randomized controlled trial (RCT).

3. Setting

One orthopedic clinic.

4. Participants

Thirty-five outpatients with grade III fresh ATFL isolated injury who received conservative therapy from April 2008 to March 2009.

5. Intervention

Treatment lasted approximately two weeks.

Arm 1: loxoprofen sodium 60–180 mg/day (n=18 [18 legs]).

Arm 2: TSUMURA Jidabokuippo (治打撲一方) Extract Granules 2.5–7.5 g/day (n=17 [17 legs]).

The dose was calculated per kg of body weight.

6. Main outcome measures

Pain (visual analogue scale [VAS]), swelling (average circumference at 5-cm centrally and peripherally from the ATFL rupture site).

7. Main results

The pain had resolved within three weeks of trauma in 12 patients, within four weeks in 2, within six weeks in 2, and within 12 weeks in 2 in Arm 1 and within three weeks in 11, within four weeks in 4, within six weeks in 1, and within 12 weeks in 1 in Arm 2. The swelling had resolved within three weeks in 9 patients, within four weeks in 4, within six weeks in 3, and within 12 weeks in 2 in Arm 1 and within three weeks in 12, within four weeks in 2, within six weeks in 2, and within 12 weeks in 1 in Arm 2. A tendency toward earlier resolution of swelling was found in Arm 2 at 2 weeks after trauma, and eventually disappeared.

8. Conclusions

The efficacy of the Western medicine and the Kampo medicine (jidabokuippo) for pain and swelling in grade III fresh ATFL isolated injury is comparable. The jidabokuippo treatment tends to resolve swelling earlier.

9. From Kampo medicine perspective

None.

10. Safety assessment in the article

Clinical testing was not carried out and there were no adverse events.

11. Abstractor's comments

This paper is clinically significant because it compares the efficacy of loxoprofen sodium with that of jidabokuippo for pain and swelling in grade III fresh ATFL isolated injury in an RCT. Unfortunately, statistical analysis between groups was not sufficiently powerful to distinguish between the groups. However, from the viewpoint of primary care for grade III fresh lateral ligament injury of the ankle joint, the results of this paper are clinically quite significant, and further clinical study is anticipated.

12. Abstractor and date

Kogure T, 6 January 2011.

Nervous System Diseases (including Alzheimer's Disease)

References

Monji A, Takita M, Samejima T, et al. Effect of yokukansan on the behavioral and psychological symptoms of dementia in elderly patients with Alzheimer's disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2009; 33: 308-11.

Monji A, Kanba S. Effectiveness of yokukansan (抑肝散) on BPSD in Alzheimer's disease — Results of a long-term antipsychotic combination trial at a department of neuropsychiatry in Kyushu*. *No 21* (*Brain 21*) 2009; 12: 446-51 (in Japanese).

1. Objectives

To evaluate the efficacy and safety of yokukansan (抑肝散) in the treatment of behavioral and psychological symptoms of dementia (BPSD) in elderly patients with Alzheimer's disease

2. Design

Randomized controlled trial (RCT)

3. Setting

Kyushu University and its affiliated hospitals (number of institutions, not specified)

4. Participants

Fifteen patients (2 males and 13 females, mean age 80.2±4.0 years) who were diagnosed with dementia and Alzheimer's disease based on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and National Institute of Neurological and Communicative Disorders and Stroke / the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, respectively, and had a Mini-Mental State Examination (MMSE) score of 6 to 23 and a Neuropsychiatric Inventory (NPI) score of 6 or higher after 2 weeks of pre-study treatment with sulpiride 50 mg/day

5. Intervention

Arm 1: Continuation of oral sulpiride 50 mg/day plus treatment with oral yokukansan (抑肝散; manufacturer, not specified) 2.5 g (containing 1.5 g of extracts) t.i.d. for 12 weeks (n=10)

Arm 2: Continuation of oral sulpiride 50 mg/day alone (n=5).

During the evaluations performed every 4 weeks, the dose of sulpiride was increased when any NPI subscore was 8 or higher and decreased when all NPI subscores were below 4.

6. Main outcome measures

BPSD and cognitive functions were evaluated using the NPI and MMSE, respectively. The Barthel Index was used for the evaluation of activities of daily living. Patients were evaluated at baseline, 4, 8, and 12 weeks.

7. Main results

One patient in arm 2 was excluded due to severe edema. NPI was significantly improved at 8 and 12 weeks compared with the baseline in arm 1 ($P<0.001$), whereas no change was observed in arm 2. The dose of sulpiride at 12 weeks was less, but not significantly less, in arm 1 than in arm 2. There were no changes in MMSE and Barthel Index from the baseline in both arms.

8. Conclusions

Yokukansan improves BPSD in elderly patients with Alzheimer's disease and can reduce the dose of antipsychotics.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

Hypokalemia was reported in 2 patients in arm 1. In addition, extrapyramidal symptoms developed and the dose of sulpiride was decreased from 150 mg/day to 100 mg/day in one patient in arm 1.

11. Abstractor's comments

This is a valuable clinical study that evaluated the efficacy of yokukansan in elderly patients with Alzheimer's disease over 12 weeks from various aspects, including behavioral and psychological symptoms, cognitive functions, and activities of daily living. Because patients in both arms were prescribed sulpiride at baseline and yokukansan was evaluated in an add-on design, there is a possibility that the efficacy of yokukansan alone was not adequately evaluated. The differences in NPI and MMSE score from those in arm 2 were not significant owing to the small number of patients. However, the trend in these scores over time suggests that significant improvements over baseline might be found if more patients were included. Even in a small population, it is suggested that yokukansan may improve NPI and reduce the dose of antipsychotics. In the future, the efficacy of yokukansan in the field of psychiatry could be more convincingly demonstrated by increasing the number of patients and selecting the appropriate control agent.

12. Abstractor and date

Goto H, 1 June 2010, 1 February 2011

Symptoms and Signs

References

Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery. *Kampo to Meneki Arerugi* (*Kampo and Immuno-Allergy*) 2008; 22: 43-55 (in Japanese with English abstract).

1. Objectives

To evaluate the efficacy of bakumondoto (麦門冬湯) on improvement in cough after lung cancer surgery

2. Design

Randomized controlled trial using sealed envelopes for allocation (RCT-envelope)

3. Setting

One hospital

4. Participants

Thirty-two outpatients with prolonged cough for more than three weeks after lung cancer surgery, who were recruited between November 2005 and December 2007. Patients with apparent respiratory disease or antitussive drug use were excluded.

5. Intervention

The duration of administration was 4 weeks.

Arm 1: TSUMURA Bakumondoto (麦門冬湯) Extract Granules (TJ-29) 9.0 g/day, n=17.

Arm 2: Medicon (dextromethorphan) 90 mg/day, or Astomine (dimemorfan) 60 mg/day, n=15.

6. Main outcome measures

Cough points, QOL score (36-Item Short Form [SF-36] v2 Health Survey)

7. Main results

Cough points showed significant decrease after 5 days of administration in arm 2, and after 3 days in arm 1 (P<0.05). Also, cough frequency was significantly less in arm 1 compared to arm 2 after 6 days of treatment until the end of the 4-week observation period (P<0.05). As for effect of improvement in cough, cough points decreased from 7 to 3.76 in arm 1, and from 7.2 to 4.58 in average after 4 weeks of administration. Cough disappeared in 3 patients in arm 1. Of 5 non-responders in arm 1, 3 showed improvement with proton pump inhibitor (PPI). QOL scores of the patients at the baseline were much lower than that of national standard. After the treatment, arm 2 showed improvement only in physical components, whereas arm 1 showed statistical improvements in general health, in both physical and mental components; mental health was significantly better in arm 1 compared to arm 2.

8. Conclusions

Bakumondoto is effective in improving not only prolonged cough after lung cancer surgery, but also mental health components in QOL, when compared with Medicon or Astomine.

9. From Kampo medicine perspective

None

10. Safety assessment in the article

None

11. Abstractor's comments

This paper demonstrated that bakumondoto not only has efficacy in reducing cough frequency in cases of prolonged cough after lung cancer surgery but also has efficacy in reducing psychological stress. Bakumondoto treatment eliminated the symptoms of cough in 3 patients and use of PPI improved cough in 3 patients; the high rates were interesting. Another report by Tsunezuka based on this study (Tsunezuka Y. The efficacy of bakumondoto on prolonged cough after lung cancer surgery — QOL analysis with 36-Item Short Form [SF-36] v2*. *Progress in Medicine* 2010; 30: 100-1 [in Japanese]), which added three months to the registration period and two patients to arm 2, also shows the same efficacy.

12. Abstractor and date

Fujisawa M, 1 June 2010, 14 January 2011